Remarks

Previously numbered claims 17-21, 23, 28-33, 44, 46-58, 64-66, 71-74, 77-81, 84, 85, 89, 90, 95, 96 and 98 were pending in this application. These claims are now renumbered because claim 16 was missing from the claims as originally filed. As a result, these claims now correspond to claims 16-20, 22, 27-32, 43, 45-57, 63-65, 70-73, 76-80, 83, 84, 88, 89, 94, 95 and 97. These claims are amended to correct claim numbering, claim dependencies and typographical errors.

Claims 6 and 7 are cancelled.

Claims 5, 13, 15, 45-57, 63-65, 70-73, 76-80, 83, 84, 88-89, 94, 95 and 97 are withdrawn. Applicant requests rejoinder of Group III claims provided such claims depend from or otherwise include all the limitations of allowable Group I claims.

Claim 99 is added. Support for this claim can be found in the specification on page 11, line 18.

Claims 1-4, 8-12, 14, 16-20, 22, 27-32, 43 and 99 are pending for examination with claim 1 being an independent claim.

No new matter has been added.

Objections to the Specification

The Examiner has requested that trademarks on pages 88 and 95 should be identified as such and accompanied by generic terminology where possible. The trademarks identified by Applicant on these pages are accompanied by a registration mark and thus are identified as trademarks. Applicant is not aware of the generic terminology for such marks.

The table on page 89 is objected to for being incorrectly titled "Table 1". This was a typographical error. The title of the table has been amended to recite "Table 5".

The reference citation on page 91 is objected to for being incomplete. The citation has been amended to include page numbers.

No new matter has been added.

Reconsideration and withdrawal of these objections is respectfully requested.

Double Patenting Rejection

Claims 1-4, 8-11, 16-20, 29-32 and 43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46, 52-56 and 58-60 of copending Application No. 10/816,220. The Examiner acknowledges that the claims are not identical but states that SEQ ID NO:1 of the instant specification is identical to SEQ ID NO:152 set forth in claim 56 of Application 10/816,220.

Without conceding the Examiner's position, Applicant defers substantive rebuttal until the cited application is allowed.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 1-4, 8-11, 16-20, 29-32 and 43 are rejected under 35 U.S.C. §112, first paragraph, enablement. The Examiner acknowledges that "the claims are directed to a composition comprising ... SEQ ID NO:1". However, according to the Examiner, "(b)ased on the components of the composition it would appear that the intended use of the claimed composition is for in vivo use in a method to treat cancer in a subject". Since "none of the examples set forth in the specification disclose the use of the claimed composition, that being a SEQ ID NO:1 and a cancer antigen with any of the other possible components (cytokines, adjuvants, mucosal adjuvants and anti-cancer agents, etc) for treatment of a cancer in a subject", the Examiner considers the claims not enabled.

Applicant respectfully traverses for the reasons set forth below.

The enablement requirement is satisfied if one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation, based on the specification and the knowledge in the art at the time of filing. The experimentation required to make and use the claimed invention may be complex, and still not undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive. The analysis of these factors

as presented below illustrates that the experimentation required to practice the invention is not undue.

Nature of the invention: The invention relates to nucleic acids that comprise a defined nucleotide sequence (i.e., SEQ ID NO:1). These nucleic acids are, by definition, immunostimulatory.

Breadth of the claims: The claimed invention is a composition comprising a nucleic acid comprising a defined nucleotide sequence (i.e., SEQ ID NO:1). The composition may further comprise other elements such as antigens, adjuvants, and other disease-specific agents. The claimed compositions can be used to stimulate immune responses but they are not limited to any particular in vitro or in vivo use. Thus they can be used therapeutically or non-therapeutically.

State of the art: The state of the art at the time of filing was aware of immunostimulatory nucleic acids, including CpG immunostimulatory nucleic acids. The immunostimulatory properties of a number of CpG immunostimulatory nucleic acids were also known in the art. (See, for example, USPs 6,194,388 and 6,207,646, both filed and issued prior to the effective filing date of the instant application, both of which disclose the ability of immunostimulatory nucleic acids to stimulate innate and antigen-specific immune responses.) The art was therefore familiar with how to make nucleic acids (including those comprising a defined nucleotide sequence) and how to use such nucleic acids to stimulate immune responses in vitro or in vivo.

Level of ordinary skill in the art: One of ordinary skill in the art would be able to make and use the claimed nucleic acids based on the level of ordinary skill. Such a person would be familiar with nucleic acid synthesis and ways of contacting immune cells with nucleic acids either in vitro or in vivo.

Level of predictability in the art: As stated above, the art was familiar with the existence of CpG containing nucleic acids capable of immunostimulation and therefore the ability to make and use CpG containing nucleic acids for immunostimulation would not be considered unpredictable.

The Examiner however states that the "state of the art with regard to cancer is unpredictable". To support her position, the Examiner cites Ezzell and Forni et al. for the proposition that "tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes". Respectfully, treatment of cancer is not a limitation of the claimed invention and the Examiner has put forth an enablement standard in

excess of what the law requires. Notwithstanding this however Applicant points out that the claimed nucleic acids induce antigen-specific as well as innate (antigen-nonspecific) immune responses. Applicant further notes that CpG nucleic acids have shown therapeutic utility in the treatment of cancers as evidenced by the references cited in Appendix A and in particular USP 6,653,292 specifically directed to use of CpG nucleic acids in the treatment of cancer.

The Examiner cites Chatterjee et al. (*Cancer Immunol Immunother.* (1994) 38:75-82) as teaching that "it has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to the bedside) is a quantum leap." The Chatterjee et al. reference is directed to anti-idiotypic antibody therapy and not immunostimulatory nucleic acid based therapy. The cited statement also refers to "novel" therapies presumably meaning therapies that have not been tested in human subjects. Again, this is not the case with CpG immunostimulatory nucleic acids. Therefore, the significance of the Chatterjee et al. teaching is tenuous at best.

The Examiner cites McCluskie et al. (*Vaccine* (2001), 19:2657-2660) as teaching that "T-rich immunostimulatory nucleic acids do not induce an immune response". The Examiner's reliance on the teachings of McCluskie et al. is unclear particularly since none of the sequences analyzed in the reference contain SEQ ID NO:1. Applicant notes that the CpG nucleic acid analyzed by McCluskie et al. (i.e., 1826) did induce an immune response, thereby supporting Applicant's contention that immune stimulation by CpG nucleic acids is not unpredictable.

With respect to the Examiner's assertions regarding in vitro/in vivo and mouse/human correlation, Applicant again refers the Examiner to references in Appendix A which support therapeutic activity of CpG nucleic acids inter alia in vivo in human subjects.

Amount of direction provided by the inventor(s): Applicant teaches how to make the invention. The nucleotide sequence of SEQ ID NO:1 is provided. The art was familiar with how to make oligonucleotides of a defined or random sequence and of a particular backbone composition. In support, the specification teaches "the oligonucleotides of the invention can be synthesized *de novo* using any of a number of procedures well known in the art" and it further sets forth a number of examples. (See page 21, line 16.) The specification also provides detailed instructions for introducing modifications into an oligonucleotide. (See pages 15-21.) The combination of an oligonucleotide and another agent such as an antigen, an adjuvant, an anti-cancer agent, and the like, would also be clear based at least on the teaching in the specification

which provides examples of each category of agent to be combined with the claimed nucleic acids. A person of ordinary skill in the art would know how to make such combinations.

Applicant teaches how to use the invention. The ability of a number of CpG immunostimulatory nucleic acids to stimulate immune responses was known at the time of filing. The specification teaches how to formulate, dose and administer the claimed nucleic acids, to whom to administer the claimed nucleic acids. (See pages 81–88.) The specification as well as the knowledge in the art at the time of filing provides guidance as to how to determine if immunostimulation has occurred in a subject.

Working examples: As acknowledged by the Examiner, the specification provides a number of working examples demonstrating the immunostimulatory properties of the claimed nucleic acids. (See pages 7-8 of Office Action.) The Examples show inter alia the ability of the claimed nucleic acids to activate B cells in vitro as indicated by proliferation (FIGs. 1, 7 and 12) and surface marker activation (FIG. 6), to stimulate secretion of Th1 cytokines such as IFN-alpha, IP-10 and IL-10 by PBMC in vitro (FIGs. 2-4, 8-11 and 13), to induce NK lytic activity in vitro (FIG. 14), and to stimulate antigen-specific antibody production in vivo when administered with an antigen (FIG. 15).

The claimed composition is not limited by a recited use. MPEP 2164.01(c) sets forth that "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use". The MPEP further states that "if any use is enabled when multiple uses are disclosed, then application is enabling for the claimed invention". (Id.) Applicant has demonstrated that the claimed composition induces immune responses in vivo and in vitro. Applicant has further demonstrated that the claimed composition induces antigen-specific as well as innate immune responses. Accordingly, Applicant has shown how to use the claimed composition by way of working example.

The Examiner states that "(t)here is no evidence of in vivo use of the claimed composition comprising SEQ ID NO:1, cancer antigen, with any of the other additional components" and that "the specification does not predict or teach any positive therapeutic benefit (i.e., treating or preventing cancer or immune response) correlated with the administration of the claimed composition in a rodent or non-rodent subject". As stated above, Applicant has demonstrated by working example that the claimed nucleic acid is capable of stimulating

immune responses in vivo and in vitro. These working examples correlate with the entire scope of the claimed composition, and the specification therefore enables the claimed invention. MPEP 2164.01(c). If the Examiner is suggesting that the addition of another agent to the nucleic acid (and optionally an antigen) interferes with immunostimulation, she is required to support that position. Moreover, Applicant is not required to demonstrate treatment or prevention of cancer as the claimed invention is not so limited.

Quantity of experimentation needed to practice the invention: In view of the teaching of the instant application and the state of the art at the time of filing, Applicant submits that the claimed invention can be practiced without undue experimentation. Applicant has identified the nucleotide sequence that confers immunostimulatory capacity on a nucleic acid and has taught how to use that nucleic acid to stimulate immune responses in vitro and in vivo.

In view of the foregoing, the specification enables the invention as claimed (i.e., a composition comprising a nucleic acid comprising SEQ ID NO:1). Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Conclusion

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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